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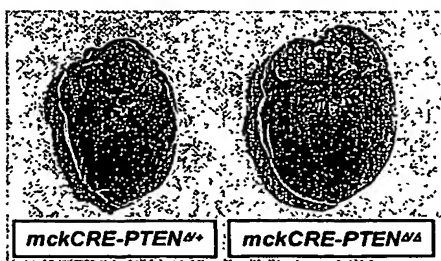
Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report:
29 July 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: COMPOSITIONS AND METHODS FOR TREATING HEART DISEASE



(57) Abstract: The PTEN/PI3K signaling pathway regulates a vast array of fundamental cellular responses. We show that cardiomyocyte-specific inactivation of tumor suppressor PTEN results in hypertrophy, and unexpectedly, a dramatic decrease in cardiac contractility. Analysis of double mutant mice revealed that the cardiac hypertrophy and the contractility defects can be genetically uncoupled. PI3K γ mediates the alteration in cell size while PI3K γ acts as a negative regulator of cardiac contractility. Mechanistically, PI3K γ inhibits cAMP production and hypercontractility can be reverted by blocking cAMP function. These data show that PTEN has an important *in vivo* role in cardiomyocyte hypertrophy and GPCR signaling and identify a function for the PTEN-PI3K pathway in the modulation of heart muscle contractility.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 03/01387

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/5375 A61K31/353 A61K31/343 A61K31/352 A61P9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, EMBASE, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00/03746 A (BRIGHAM & WOMENS HOSPITAL) 27 January 2000 (2000-01-27) page 21, line 16; claims 1,16,17,61,62 -----	1,2,4,5, 7-11

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

19 March 2004

Date of mailing of the international search report

09. 06. 2004

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 03/01387

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 4-8 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.
2. ☒ Claims Nos.: 10,11
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1, 2, 4, 5, 7-11 all in part

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 4-8 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.

Continuation of Box I.2

Claims Nos.: 10,11

Present claims 1 and 2 relate to an extremely large number of uses of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds disclosed in claim 3.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1, 2, 4, 5, 7-11 all in part

The use of an inactive PI3Kgamma or an inactive fragment of PI3Kgamma for the treatment of a heart disease

2. claims: 1, 2, 4, 5, 7-11 all in part

The use of an antibody of PI3Kgamma for the treatment of a heart disease

3. claims: 1, 2, 4, 5, 7-11 all in part

The use of an antisense oligonucleotide that inhibits the expression of PI3Kgamma for the treatment of a heart disease

4. claims: 1, 3, 4, 6-11 all in part

The use of wortmannin for the treatment of a heart disease

5. claims: 1, 3, 4, 6-11 all in part

The use of LY294002 for the treatment of a heart disease

6. claims: 1, 3, 4, 6-11 all in part

The use of quercetin for the treatment of a heart disease

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 03/01387

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0003746	A	27-01-2000	US 2002082281 A1	27-06-2002
			AU 4990599 A	07-02-2000
			WO 0003746 A2	27-01-2000
			US 2003013703 A1	16-01-2003
